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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,195	11/14/2003	Joffre B. Baker	GHDX-005	5745

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EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,195	BAKER ET AL.	
	Examiner	Art Unit	
	Amanda Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66 and 68-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66 and 68-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/26/2010 & 5/25/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 25, 2010 has been entered.

Claims 66, 68- are currently pending.

Claims 66, 71, and 82 have been amended.

Declarations

2. The declaration under 37 CFR 1.132 filed May 25, 2010 by Steve Shak is insufficient to overcome the enablement rejection set forth in the last Office action. A detailed explanation is presented below in paragraph 5.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on March 26, 2010 and May 25, 2010 have been received. The references listed in the IDS have been reviewed as indicated on the 1449, and a copy is attached herein.

Claim Rejections - 35 USC § 112 1st paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following rejection has been modified based on the claim amendments:

Claims 66 and 68-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Nature of the Invention

Claim 66 is drawn to a method for predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with cetuximab. Claim 66 comprises (a) assaying a normalized level of a predictive RNA transcript in a sample comprising ErbB 1 expressing colon cancer cells obtained from said patient, wherein the predictive RNA transcript is the transcript of laminin gamma 2

(LAMC2); (b) analyzing the normalized level of the LAMC2 transcript; and (c) predicting the likelihood of response of the patient to treatment with cetuximab based on the normalized level of the LAMC2 transcript, wherein an increased normalized level of LAMC2 RNA transcript correlates with resistance of the colon cancer to treatment with cetuximab. Thus the nature of the invention requires the knowledge of a reliable association between the level of LAMC2 in a sample and how a patient will respond to treatment with cetuximab.

Scope of the Claims:

Claim 66 is broadly drawn to a method for predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with cetuximab. The wherein clause states "wherein an increased normalized level of LAMC2 RNA transcript correlates with resistance of the colon cancer to treatment with cetuximab". Here the claims do not define what the increase is in comparison to. Further the claims do indicate how the increased level of LAMC2 RNA correlates with resistance to treatment with cetuximab (does increased LAMC2 RNA mean there is an increased or decreased likelihood of response to treatment with cetuximab?).

Claim 82 further comprises determining the normalized level of one or more predictive RNA transcripts in said sample, wherein the predictive RNA transcript is the transcript of one or more genes selected from the group consisting of: ErbB3; EREG; ID1; TITF1; CA9; CD44v6; DR5; KRT17; P14ARF; and PLAUR, wherein an increased normalized level of the predictive RNA transcript of one or more of CA9; CD44v6; DR5; KRT17; P14ARF; and PLAUR, indicates that the patient will show a

decreased likelihood of response to treatment with cetuximab, and an increased normalized level of the predictive RNA transcript of one or more of ErbB3; EREG; ID1; and TITF1 indicates that the patient will show an increased likelihood of response to treatment with cetuximab.

Teachings in the Specification and Examples:

The specification (page 25) teaches that EGFR (also known as ErbB1) is known to be active in several tumor types such as breast, colon, and head and neck cancers. The specification also teaches that several ErbB1 inhibitors are promising drug candidates for the treatment of ErbB1 expressing cancers. In particular the specification (page 26) teaches that cetuximab is a monoclonal antibody that blocks the ErbB1 and ErbB1 -dependent cell growth that is currently being tested in phase III clinical trials.

The specification teaches (Example 2) that twenty-three colon adenocarcinoma patients in all were studied using a 192-gene assay. Following treatment with an unspecified EGFR inhibitor, three patients were determined to have had a partial response, five to have stable disease, and fifteen to have progressive disease.

Table 3 shows the results obtained using the partial response criterion. LAMC2, ErbB3; EREG; ID1; TITF1; CA9; DR5; KRT17; P14ARF; and PLAUR were found to be over expressed. The following genes had negative responses: LAMC2 (p=0.0357), CA9 (p=0.0267), DR5 (p=0.0767), KRT17 (p=0.0513), P14ARF (p=0.022), and PLAUR (p=0.0983). The following genes had negative responses: ErbB3 (p=0.1401), EREG (p=0.0333), IDI (p=0.0498), TITF1 (p=0.1211). Here the term "negative" indicates that

greater expression of the gene decreased likelihood of response to treatment with the EGFR inhibitor, and "positive" indicates that increased expression of the gene increased likelihood of response to EGFR inhibitor (page 28). Here it is noted several of the genes (i.e., DR5, ErbB3, KRT17, PLAUR, and TITF1) did not have statistically significant p values (i.e p= <0.05) therefore the specification does not teach a reliable association between these genes and response to treatment with an EGFR inhibitor.

Table 4 shows the results obtained using the clinical response criterion. CD44v6 was found to be over expressed. CD44v6 had a negative response and a p value of 0.0047. None of the other claimed genes are listed in Table 4.

In the instant case the specification does not teach which EGFR inhibitors were used in example 2. However it is noted for the record that on April 17, 2008 the Applicants have submitted a declaration by Joffre B. Baker, PhD stating that the patients were treated with an ErbB1 inhibitor selected from erlotinib, gefitinib, cetuximab, EMD72000, and AEE788. Dr. Baker states that the results presented in tables 3 and 4 were the result of treatment with these ErbB1 inhibitors. Then on December 3, 2009 the Applicants submitted two more declarations by Joffre B. Baker, PhD and Steve Shak M.D. stating that 15 patients were treated with the ErbB1 inhibitor EMD 72000 and 8 patients were treated with cetuximab, with or without chemotherapy. The declaration further states that the three partial responders were treated with EMD72000 alone.

Thus the data presented in Table 3 is based on 15 patients treated with the ErbB1 inhibitor EMD 72000 and 8 patients were treated with cetuximab, with or without

chemotherapy. As stated above three patients were determined to have had a partial response, five to have stable disease, and fifteen to have progressive disease. Since the three partial responders were treated with EMD72000, the patients treated with cetuximab must have either had stable disease or progressive disease.

State of the Art and the Unpredictability of the Art:

The level of skill in the art is deemed to be high. However the unpredictability with regard to correlating the level of LAMC2 with a patient's response to treatment with cetuximab is even higher.

In the instant case it is highly unpredictable if one can predict the likelihood that a human colon cancer patient will exhibit a clinically beneficial response to treatment with cetuximab. For example the declaration filed by Steven Shak MD filed on May 25, 2010 refers to a graph showing the LAMC2 mRNA level for each of the 23 patients (See Exhibit 1). The graph does not indicate which of the patients received EMD 72000 and which patients received cetuximab however the graph does differentiate between the non partial responders (No PR) and the partial responders (Yes PR). Each circle represents a patient. As shown in Exhibit 1 the 3 partial responders had LAMC2 values ranging between approximately 3.1-5.25 whereas the 20 non responders had LAMC2 values ranging between approximately 3.2-7.5. Here it is noted that there is substantial overlap between the two groups. In fact 12 of the 18 non responders had LAMC2 values that fell within the 3.1-5.25 range. Based on this information it does not appear that one of skill in the art could accurately predict the likelihood that a human colon cancer patient will exhibit a clinically beneficial response to treatment with cetuximab

since 12 of the non responders would have been predicted to respond based on their LAMC2 levels.

Further it is noted that based on the declarations filed we do know that 15 patients were treated with the ErbB1 inhibitor EMD 72000 and 8 patients were treated with cetuximab, with or without chemotherapy. We also known that the three partial responders were treated with EMD72000. Since none of the patients that were given cetuximab responded to treatment we do not know what the expression level of LAMC2 would be in a patient that responded to treatment with cetuximab. The finding that the three patients who responded to EMD 72000 had lower levels of LAMC2 RNA compared to patients who did not respond or had progressive disease does not necessarily mean that patient who respond cetuximab will also have lower levels of LAMC2 RNA compared to patients who did not respond or had progressive disease. This unpredictability is discussed in a post filing date paper by Solmi et al (BMC Cancer 2008 Vol 8 page 227). Solmi teaches that they characterized HT-29 and Caco-2 human colon cancer cell lines untreated and treated with cetuximab or gefitinib alone and in combination with EGF. Solmi teaches that cetuximab has opposite effects on gene expression profiling compared to EGF alone or gefitinib, indicating a different action mechanism than the other drug, even though the cell cyto-morphological transformations are sometimes the same, possibly suggesting an important role by translational regulation on the cellular pathways (page 3). As such Solmi teaches that treatment with different EGFR inhibitors results in different gene expression patterns and therefore the findings with one drug can not be extrapolated to another drug.

It is also unpredictable as to whether an increased normalized level of DR5, KRT17, and PLAUR indicates that a patient will show a decreased likelihood of response to treatment with cetuximab because the p values for each of these genes as presented in Table 3 indicated that the results were not statistically significant. Additionally it is unpredictable as to whether an increased normalized level of ErbB3 and TITF1 indicates that the patient will show an increased likelihood of response to treatment with cetuximab because the p values for each of these genes as presented in Table 3 indicated that the results were not statistically significant. Thisted (The University of Chicago 1998) teaches that p values are needed to determine whether superior results obtained in a particular study are really superior or if they occurred by chance (page 1). Thisted teaches that it has become scientific convention to say that p values exceeding 0.05 are not statistically significant. Finally with regard to the statistically significant p-values presented in Table 3 it is noted that they are based on the data combined from 23 patients that were treated with two different drugs. The p values are not based on treatment with cetuximab alone and it is unclear how the p-value would change if the data from the 15 patients that were treated with EMB 72000 were removed.

Quantity of Experimentation:

The specification asserts that patients diagnosed with colon cancer with elevated levels of LAMC2 are less likely to respond to a treatment with cetuximab. However since none of the patients that were given cetuximab responded to treatment we do not know what the expression level of LAMC2 would be in a patient that responded to

treatment with cetuximab. Based on the data presented in the specification and the declarations that have been filed it is unpredictable if the claimed method works as such further experimentation would be required. For example, such experimentation may involve treating a large number of colon cancer patient's cetuximab, assaying the expression levels of LAMC2, and then monitoring the patients to determine disease progression. Such random, trial by error experimentation is considered to be undue. The specification has provided only an invitation to experiment.

Conclusions:

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the guidance provided by the applicant and the specific examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention.

Response to Arguments

5. Regarding the enablement rejection the Applicants statethat the Office appears to question the data and asserts that one of skill in the art could not predict the likelihood that a human colon cancer patient will exhibit a clinically beneficial response to treatment because of some overlap in LAMC2 expression level between partial responders and non-responders. However, the Applicants believe that the Office makes this assertion without any evidence and therefore fails to establish a *prima facie* case of non enablement of the claims. The Applicants state that they have provided

sufficient evidence that one skilled in the art may still predict the likelihood of cancer recurrence even though the raw data shows some overlap in gene expression levels between partial responders and non-responders overlap, if there is a statistically significant difference between the groups. The Applicants then refer to papers by Maitra and Ball which show that expression levels overlap between clinically favorable outcomes and clinically unfavorable outcomes. Further they argue that as shown in Table 3 LAMC2 levels were significantly correlated with a negative response ($p=0.0357$). Therefore one may still predict the likelihood of response even thought there was overlap in LAMC2 gene expression levels between the partial responders and the non responders.

These arguments and the declaration filed on May 25, 2010 by Steven Shak MD have been fully considered but are not persuassive. In the instant case the declaration filed by Steven Shak MD filed on May 25, 2010 refers to a graph showing the LAMC2 mRNA level for each of the 23 patients (See Exhibit 1). The graph does not indicate which of the 15 patients received EMD 72000 and which of the 8 patients received cetuximab. However we do know that only 3 patients responded to treatment and those 3 patients were given EMD 72000. Additionally it is noted that the graph differentiates between the non partial responders (No PR) and the partial responders (Yes PR) and that each circle represents a single patient. As shown in Exhibit 1 the 3 partial responders had LAMC2 values ranging between approximately 3.1-5.25 whereas the 20 non responders had LAMC2 values ranging between approximately 3.2-7.5. Here it is noted that there is substantial overlap between the two groups. In fact 12 of the 18 non

responders had LAMC2 values that fell within the 3.1-5.25 range. Based on this information in this graph it does not appear that one of skill in the art could accurately predict the likelihood that a human colon cancer patient will exhibit a clinically beneficial response to treatment with cetuximab since 12 of the non responders would have been predicted to respond based on their LAMC2 levels. With respect to the papers cited by the Applicants (Maitra et al and Ball et al) it is noted that in both of studies they compared the expression levels between patients with clinically favorable outcomes vs patients with clinically unfavorable outcomes. These papers are not analogous to the present situation because in the present study none of the patients that were given cetuximab responded to treatment and therefore we do not know what the expression level of LAMC2 would be in a patient that responded to treatment with cetuximab. As discussed above the finding that the three patients who responded to EMD 72000 had lower levels of LAMC2 RNA compared to patients who did not respond or had progressive disease does not necessarily mean that patient who respond cetuximab will also have lower levels of LAMC2 RNA compared to patients who did not respond or had progressive disease. This unpredictability is discussed in a post filing date paper by Solmi et al (BMC Cancer 2008 Vol 8 page 227). Solmi teaches that they characterized HT-29 and Caco-2 human colon cancer cell lines untreated and treated with cetuximab or gefitinib alone and in combination with EGF. Solmi teaches that cetuximab has opposite effects on gene expression profiling compared to EGF alone or gefitinib, indicating a different action mechanism than the other drug, even though the cell cyto-morphological transformations are sometimes the same, possibly suggesting an

important role by translational regulation on the cellular pathways (page 3). As such Solmi teaches that treatment with different EGFR inhibitors results in different gene expression patterns and therefore the findings with one drug can not be extrapolated to another drug. Finally the p-value presented in Table 3 for LAMC2 is based on the data combined from 23 patients that were treated with two different drugs. The p value is not based on treatment with cetuximab alone and it is unclear how the p-value would change if the data from the 15 patients that were treated with EMB 72000 were removed. For these reasons the arguments and the evidence provided by the applicants is not convincing and the enablement rejection is maintained.

Conclusion

6. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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